



STIC Search Report

Biotech-Chem Library

STIC Database Tracking Number: 125631

TO: David Venci
Location: 3d68
Art Unit: 1641
Friday, June 25, 2004

3c 70

Case Serial Number: pctus0336133

From: Mary Hale
Location: Biotech/Chem Library
Rem 1D86
Phone: 2-2507

Mary.Hale@uspto.gov

Search Notes

David,

Here are the results from the lost, now found search. Two hits were retrieved.

Enter your Search Topic Information below:

PLEASE SEARCH CLAIMS 1 AND 2. FOR A DESCRIPTION OF
"α-DICARBONYL COMPOUND," SEE SPECIFICATION P. 7, WHICH
IS ATTACHED.

Special Instructions and Other Comments:

(For fastest service, let us know the best times to contact you, in case the searcher needs further clarification on your search.)

Monday-Friday, 8am-5pm

Press ALT + F, then P to print this screen for your own information.

SEND **RESET**

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Last Modified: 04/06/2004 12:14:41

ground, and ADMA does not react with an α -dicarbonyl compound to form a

ADMA and arginine

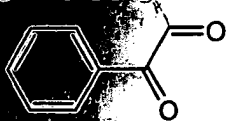
A variety of α -dicarbonyl compounds that are known in the art can be used in methods to modify guanidino nitrogens of SDMA and arginine. The structure of a α -dicarbonyl compound is shown below.

30344-0024

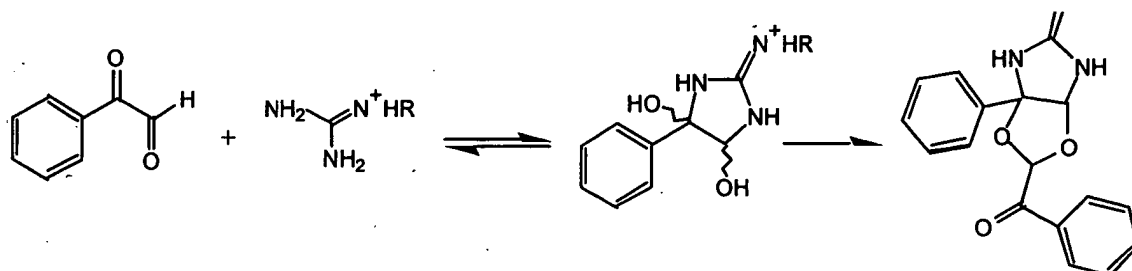
30] Suitable α -dicarbonyl compounds include, but are not limited to, dialdehydes, ketone aldehydes, and diketones. Non-limiting examples of α -dicarbonyl compounds are biacetyl, pyruvic acid, glyoxal, methylglyoxal, deoxyosones, 3-deoxyosones, malondialdehyde, 2-oxopropanal, phenylglyoxal, 2,3-butanedione, and 1,2-cyclohexanedione.

30] In many embodiments, R is a bulky group, including, but not limited to, a cyclopentyl group, a substituted cyclopentyl group; a six-membered ring, such as phenyl, a substituted phenyl (e.g., *p*-hydroxyphenylglyoxal, nitrophenylglyoxal, etc.), and the like. In embodiments of particular interest, the α -dicarbonyl compound is phenylglyoxal. The structure of phenylglyoxal is shown below.

phenylglyoxal



31] As one non-limiting example, where the α -dicarbonyl compound reaction with arginine proceeds as follows:



The reaction with SDMA proceeds in a similar way.

32] In addition to reacting with the guanidino amine of arginine, phenylglyoxal has been reported to react with the α -amino group of the peptides to give α -keto acyl peptides. Takahashi (1968) *J. Biol. Chem.* 243:6171-6179. In the context of free amino acid, this observation indicates that phenylglyoxal will react with all α -amino groups of all amino acid.

FULL ESTIMATED COST

SINCE FILE	TOTAL
ENTRY	SESSION
0.21	0.21

FILE 'REGISTRY' ENTERED AT 07:29:39 ON 25 JUN 2004
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

```
STRUCTURE FILE UPDATES: 23 JUN 2004 HIGHEST RN 698346-19-9
DICTIONARY FILE UPDATES: 23 JUN 2004 HIGHEST RN 698346-19-9
```

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
<http://www.cas.org/ONLINE/DBSS/registryss.html>

=> e guanidino nitrogen/cn 5

E1	1	GUANIDINIUM-P-NITROBENZOATE/CN
E2	1	GUANIDINO METHYLTRANSFERASE (STREPTOMYCES GRISEOCHROMOGENES GENE BLSL)/CN
E3	0 -->	GUANIDINO NITROGEN/CN
E4	1	GUANIDINO, CYANO-/CN
E5	1	GUANIDINOACETATE/CN

$$\Rightarrow e$$

E6	1	GUANIDINOACETATE AMIDINOHYDROLASE/CN
E7	1	GUANIDINOACETATE KINASE/CN
E8	1	GUANIDINOACETATE METHYLTRANSFERASE/CN
E9	1	GUANIDINOACETATE METHYLTRANSFERASE (RAT STRAIN SPRAGUE-DAWLEY)/CN
E10	1	GUANIDINOACETATE N-METHYLTRANSFERASE (HUMAN CLONE MGC:1854 IMAGE:2989341)/CN
E11	1	GUANIDINOACETATE N-METHYLTRANSFERASE (HUMAN CLONE MGC:24023 IMAGE:4246521)/CN
E12	1	GUANIDINOACETATE TRANSMETHYLASE/CN
E13	1	GUANIDINOACETIC ACID/CN
E14	1	GUANIDINOACETIC ACID γ -LACTAM/CN
E15	1	GUANIDINOACETIC ACID HYDROCHLORIDE/CN
E16	1	GUANIDINOACETYL CHLORIDE HYDROCHLORIDE/CN
E17	1	GUANIDINOACETYLGLYCINE ETHYL ESTER HYDROCHLORIDE/CN

=> s guanidino(1)nitrogen?

2013 GUANIDINO

12936 NITROGEN?

```

L1          0 GUANIDINO(L) NITROGEN?

```

=> s guanidino?/cn

L2 34 GUANIDINO?/CN

```

=> s arginine/cn
L3      2 ARGININE/CN

=> s "α-dicarbonyl"/cns
      1621184 "A"/CNS
      41993 "DICARBONYL"/CNS
L4      15 "A-DICARBONYL"/CNS
        ( ("A" (W) "DICARBONYL") /CNS)

=> s (dialdehyde? or ketoaldehyde? or diketone? or biacetyl? or pyruvic acid or
glyoxal or methylglyoxal or deoxyosone? or malondialdehyde or oxopropanol or
phenylglyoxal or butanedione or cyclohexanedione)
      313 DIALDEHYDE?
      3 KETOALDEHYDE?
      49 DIKETONE?
      53 BIACETYL?
      1821 PYRUVIC
      6421742 ACID
      8525 ACIDS
      6428081 ACID
            (ACID OR ACIDS)
      1754 PYRUVIC ACID
            (PYRUVIC (W) ACID)
      2016 GLYOXAL
      1 GLYOXALS
      2016 GLYOXAL
            (GLYOXAL OR GLYOXALS)
      103 METHYLGLYOXAL
      0 DEOXYOSONE?
      42 MALONDIALDEHYDE
      3 OXOPROPANOL
      226 PHENYLGLYOXAL
      19804 BUTANEDIONE
      11846 CYCLOHEXANEDIONE
L5      35678 (DIALDEHYDE? OR KETOALDEHYDE? OR DIKETONE? OR BIACETYL? OR PYRUV
            IC ACID OR GLYOXAL OR METHYLGLYOXAL OR DEOXYOSONE? OR MALONDIALD
            EHYDE OR OXOPROPANOL OR PHENYLGLYOXAL OR BUTANEDIONE OR CYCLOHEX
            ANEDIONE)

=> s (dialdehyde? or ketoaldehyde? or diketone? or biacetyl? or pyruvic acid or
glyoxal or methylglyoxal or deoxyosone? or malondialdehyde or oxopropanol or
phenylglyoxal or butanedione or cyclohexanedione)/cn
      22 DIALDEHYDE?/CN
      0 KETOALDEHYDE?/CN
      2 DIKETONE?/CN
      42 BIACETYL?/CN
      1 PYRUVIC ACID/CN
      1 GLYOXAL/CN
      1 METHYLGLYOXAL/CN
      0 DEOXYOSONE?/CN
      1 MALONDIALDEHYDE/CN
      0 OXOPROPANOL/CN
      1 PHENYLGLYOXAL/CN
      1 BUTANEDIONE/CN
      1 CYCLOHEXANEDIONE/CN
L6      72 (DIALDEHYDE? OR KETOALDEHYDE? OR DIKETONE? OR BIACETYL? OR PYRUV
            IC ACID OR GLYOXAL OR METHYLGLYOXAL OR DEOXYOSONE? OR MALONDIALD
            EHYDE OR OXOPROPANOL OR PHENYLGLYOXAL OR BUTANEDIONE OR CYCLOHEX
            ANEDIONE)/CN

=> e sdma/cn 5
E1      1      SDM 79/CN

```

```
E2          1      SDM 801/CN
E3          3 --> SDMA/CN
E4          1      SDMA (REDUCING AGENT)/CN
E5          1      SDMF (HUMAN FETAL HEART REDUCED)/CN
```

```
=> s e3;d 1 cbib abs
L7          3 SDMA/CN
```

'CBIB' IS NOT A VALID FORMAT FOR FILE 'REGISTRY'
'ABS' IS NOT A VALID FORMAT FOR FILE 'REGISTRY'

The following are valid formats:

Substance information can be displayed by requesting individual fields or predefined formats. The predefined substance formats are: (RN = CAS Registry Number)

```
REG      - RN
SAM      - Index Name, MF, and structure - no RN
FIDE     - All substance data, except sequence data
IDE      - FIDE, but only 50 names
SQIDE    - IDE, plus sequence data
SQIDE3   - Same as SQIDE, but 3-letter amino acid codes are used
SQD      - Protein sequence data, includes RN
SQD3     - Same as SQD, but 3-letter amino acid codes are used
SQN      - Protein sequence name information, includes RN

CALC     - Table of calculated properties
EPROP    - Table of experimental properties
PROP     - EPROP and CALC
```

Any CA File format may be combined with any substance format to obtain CA references citing the substance. The substance formats must be cited first. The CA File predefined formats are:

```
ABS  -- Abstract
APPS -- Application and Priority Information
BIB  -- CA Accession Number, plus Bibliographic Data
CAN  -- CA Accession Number
CBIB -- CA Accession Number, plus Bibliographic Data (compressed)
IND  -- Index Data
IPC  -- International Patent Classification
PATS -- PI, SO
STD  -- BIB, IPC, and NCL

IABS -- ABS, indented, with text labels
IBIB -- BIB, indented, with text labels
ISTD -- STD format, indented

OBIB ----- AN, plus Bibliographic Data (original)
OIBIB ----- OBIB, indented with text labels

SBIB ----- BIB, no citations
SIBIB ----- IBIB, no citations
```

The ALL format gives FIDE BIB ABS IND RE, plus sequence data when it is available.

The MAX format is the same as ALL.

The IALL format is the same as ALL with BIB ABS and IND indented, with text labels.

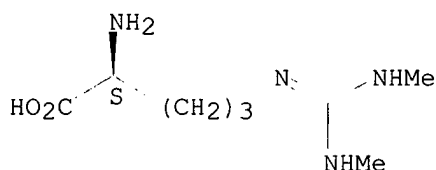
For additional information, please consult the following help messages:

HELP DFIELDS -- To see a complete list of individual display fields.
HELP FORMATS -- To see detailed descriptions of the predefined formats.
ENTER DISPLAY FORMAT (IDE):end

=> d ide 1

L7 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN 30344-00-4 REGISTRY
CN L-Ornithine, N5-[bis(methylamino)methylene]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ornithine, N5-(N,N'-dimethylamidino)-, L- (8CI)
OTHER NAMES:
CN SDMA
CN Symmetric dimethylarginine
FS STEREOSEARCH
DR 100663-65-8
MF C8 H18 N4 O2
LC STN Files: ANABSTR, BEILSTEIN*, BIOSIS, CA, CANCERLIT, CAPLUS, EMBASE,
MEDLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
DT.CA Caplus document type: Conference; Journal; Patent
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study);
PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological
study); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological
study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP
(Preparation); PROC (Process); PRP (Properties); RACT (Reactant or
reagent); USES (Uses)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

96 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
98 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> fil medl,hcap,biosis,embase,jicst,wpids

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	154.91	155.12

FILE 'MEDLINE' ENTERED AT 07:33:11 ON 25 JUN 2004

FILE 'HCAPLUS' ENTERED AT 07:33:11 ON 25 JUN 2004

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Searched by: Mary Hale 571-272-2507 REM 1D86

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FILE 'BIOSIS' ENTERED AT 07:33:11 ON 25 JUN 2004
COPYRIGHT (C) 2004 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'EMBASE' ENTERED AT 07:33:11 ON 25 JUN 2004
COPYRIGHT (C) 2004 Elsevier Inc. All rights reserved.

FILE 'JICST-EPLUS' ENTERED AT 07:33:11 ON 25 JUN 2004
COPYRIGHT (C) 2004 Japan Science and Technology Agency (JST)

FILE 'WPIDS' ENTERED AT 07:33:11 ON 25 JUN 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

=> s (sdma or symmetric dimethylarginine or 30344-00-4) and (l2 or guanidin?) (l)nitrogen and (l3 or arginine?)

L8 1 FILE MEDLINE
L9 1 FILE HCAPLUS
L10 0 FILE BIOSIS
L11 1 FILE EMBASE
L12 0 FILE JICST-EPLUS
L13 1 FILE WPIDS

TOTAL FOR ALL FILES

L14 4 (SDMA OR SYMMETRIC DIMETHYLARGININE OR 30344-00-4) AND (L2 OR GUANIDIN?) (L) NITROGEN AND (L3 OR ARGININE?)

=> dup rem l14

PROCESSING COMPLETED FOR L14

L15 2 DUP REM L14 (2 DUPLICATES REMOVED)

=> d 1-2 cbib abs hitstr

'HITSTR' IS NOT A VALID FORMAT

In a multifile environment, a format can only be used if it is valid in at least one of the files. Refer to file specific help messages or the STNGUIDE file for information on formats available in individual files.

REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):cbib abs

L15 ANSWER 1 OF 2 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2004-431969 [40] WPIDS

AB WO2004046314 A UPAB: 20040624

NOVELTY - Detecting (M1) asymmetric dimethyl-**arginine** (ADMA) in sample containing ADMA, symmetric dimethyl-**arginine** (**SDMA**) and **arginine**, involves contacting sample with alpha -dicarbonyl compound, which results in modification of **guanidino nitrogens** of **SDMA** and **arginine**, to produce modified **SDMA** and modified **arginine**, and detecting ADMA in sample, where sample is suspected of containing ADMA, and **SDMA** or **arginine**.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) an antibody (I) binding specifically to ADMA;

(2) antibody binding specifically to modified **SDMA**, where the **guanidino nitrogens** of the **SDMA** are modified by reaction with an alpha -dicarbonyl compound; and

(3) kit (II) for carrying out (M1), comprises an alpha -dicarbonyl agent that modifies the **guanidino nitrogens** of **SDMA** and the **guanidino nitrogens** of **arginine**, and an antibody that binds to ADMA.

USE - (M1) is useful for detecting ADMA in a sample comprising ADMA, **SDMA** and **arginine** (claimed).

(M1) is useful for diagnosing various disorders such as hypertension, hyperhomocysteinemia, hyperglycemia, hypercholesterolemia, insulin resistance, renal insufficiency, congestive heart failure, atherosclerosis, transplant arteriopathy, by determining the level of ADMA in a biological sample. (M1) is useful for determining the extent, severity, progression or stage of a disorder for which an elevated ADMA level is diagnostic, for monitoring progression, or efficacy of a treatment, of a disorder for which ADMA level is diagnostic.

ADVANTAGE - (M1) enables detection of ADMA in a sample.

Dwg.0/0

L15 ANSWER 2 OF 2 MEDLINE on STN DUPLICATE 1
 2001190656. PubMed ID: 11129410. Asymmetric dimethylarginine, derangements of the endothelial nitric oxide synthase pathway, and cardiovascular diseases. Boger R H; Bode-Boger S M. (Institute of Clinical Pharmacology, Medical School, Hannover, Germany.. boeger.rainer@mh-hannover.de) . Seminars in thrombosis and hemostasis, (2000) 26 (5) 539-45. Ref: 54. Journal code: 0431155. ISSN: 0094-6176. Pub. country: United States. Language: English.

AB Analogues of L-**arginine** that are chemically modified at the terminal **guanidino nitrogen** group, such as Nomega-monomethyl-L-**arginine** (L-NMMA), have been used for nitric oxide synthase inhibition. However, L-NMMA and other methylated L-**arginine** analogues are also endogenously formed. Among these, asymmetric dimethylarginine (ADMA) and **symmetric dimethylarginine** (SDMA) have been shown to be the most abundant. Like L-NMMA, ADMA is an inhibitor of NO synthase, whereas SDMA is inactive. ADMA is synthesized by N-methyltransferases, a family of enzymes that methylate L-**arginine** residues within specific proteins. Free ADMA is released during proteolytic cleavage of methylated proteins; it can be detected in plasma and urine, but its intracellular concentrations appear to be much higher. ADMA is metabolized by the enzyme dimethylarginine dimethylaminohydrolase (DDAH), and inhibition of DDAH activity has been shown to lead to increased ADMA levels and endothelial dysfunction. Plasma levels of ADMA are elevated in endstage renal failure, in atherosclerosis and hypercholesterolemia, in hypertension, and in heart failure. Although the molecular cause for elevation of ADMA concentration in these diseases has not been fully elucidated, evidence is accumulating that ADMA is one cause of endothelial dysfunction in these diseases. Moreover, it may be a marker or even a risk factor for cardiovascular disease. Therefore, pharmacological modulation of ADMA concentration may be a novel therapeutic target in cardiovascular diseases.

RC633.S3

=> s (dialdehyde? or ketoaldehyde? or diketone? or biacetyl? or pyruvic acid or glyoxal or methylglyoxal or deoxyosone? or malondialdehyde or oxopropanol or phenylglyoxal or butanedione or cyclohexanedione or 14 or 15 or dicarbonyl?)) UNMATCHED RIGHT PARENTHESIS 'CARBONYL?))'
 The number of right parentheses in a query must be equal to the number of left parentheses.

=> s (dialdehyde? or ketoaldehyde? or diketone? or biacetyl? or pyruvic acid or glyoxal or methylglyoxal or deoxyosone? or malondialdehyde or oxopropanol or phenylglyoxal or butanedione or cyclohexanedione or 14 or 15 or dicarbonyl?)
 TOO MANY TERMS FOR FILE CROSSOVER IN L5
 There are limits on the size of an answer set being crossed over from one file to another. Enter HELP CROSSOVER at an arrow prompt (=>) for specific information.

=> s (dialdehyde? or ketoaldehyde? or diketone? or biacetyl? or pyruvic acid or glyoxal or methylglyoxal or deoxyosone? or malondialdehyde or oxopropanol or phenylglyoxal or butanedione or cyclohexanedione or 14 or dicarbonyl or 16)

Searched by: Mary Hale 571-272-2507 REM 1D86

L16 20245 FILE MEDLINE
L17 112591 FILE HCAPLUS
L18 21049 FILE BIOSIS
L19 23002 FILE EMBASE
L20 11554 FILE JICST-EPLUS
L21 10618 FILE WPIDS

TOTAL FOR ALL FILES

L22 199059 (DIALDEHYDE? OR KETOALDEHYDE? OR DIKETONE? OR BIACETYL? OR PYRUVIC ACID OR GLYOXAL OR METHYLGLYOXAL OR DEOXYOSONE? OR MALONDIALDEHYDE OR OXOPROPANOL OR PHENYLGLYOXAL OR BUTANEDIONE OR CYCLOHEXANEDIONE OR L4 OR DICARBONYL OR L6)

=> s (sdma or symmetric dimethylarginine or 30344-00-4 or l2 or guanidin? or l3 or arginine?) and l22

L23 1400 FILE MEDLINE
L24 2935 FILE HCAPLUS
L25 1226 FILE BIOSIS
L26 913 FILE EMBASE
L27 71 FILE JICST-EPLUS
L28 162 FILE WPIDS

TOTAL FOR ALL FILES

L29 6707 (SDMA OR SYMMETRIC DIMETHYLARGININE OR 30344-00-4 OR L2 OR GUANIDIN? OR L3 OR ARGinine?) AND L22

=> s (sdma or symmetric dimethylarginine or 30344-00-4 or l2 or guanidin?) and (l3 or arginine?) and l22

L30 65 FILE MEDLINE
L31 187 FILE HCAPLUS
L32 60 FILE BIOSIS
L33 44 FILE EMBASE
L34 1 FILE JICST-EPLUS
L35 9 FILE WPIDS

TOTAL FOR ALL FILES

L36 366 (SDMA OR SYMMETRIC DIMETHYLARGININE OR 30344-00-4 OR L2 OR GUANIDIN?) AND (L3 OR ARGinine?) AND L22

=> s l36 and modif?

L37 31 FILE MEDLINE
L38 88 FILE HCAPLUS
L39 38 FILE BIOSIS
L40 24 FILE EMBASE
L41 0 FILE JICST-EPLUS
L42 1 FILE WPIDS

TOTAL FOR ALL FILES

L43 182 L36 AND MODIF?

=> s (sdma or symmetric dimethylarginine or 30344-00-4) and (l2 or guanidin?) and (l3 or arginine?) and nitrogen and l22

L44 0 FILE MEDLINE
L45 0 FILE HCAPLUS
L46 0 FILE BIOSIS
L47 0 FILE EMBASE
L48 0 FILE JICST-EPLUS
L49 1 FILE WPIDS

TOTAL FOR ALL FILES

L50 1 (SDMA OR SYMMETRIC DIMETHYLARGININE OR 30344-00-4) AND (L2 OR GUANIDIN?) AND (L3 OR ARGinine?) AND NITROGEN AND L22

=> d

L50 ANSWER 1 OF 1 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-431969 [40] WPIDS
DNN N2004-341454 DNC C2004-161888
TI Detecting asymmetric dimethyl-**arginine** (ADMA) in sample having
ADMA, symmetric dimethyl-**arginine** (**SDMA**) and
arginine, for diagnosing hyperglycemia, by detecting ADMA after
modifying **SDMA** and **arginine** using alpha-
dicarbonyl compound.
DC B04 D16 S03
IN COOKE, J; LIN, K Y
PA (STRD) UNIV LELAND STANFORD JUNIOR
CYC 107
PI WO 2004046314 A2 20040603 (200440)* EN 28 C12N000-00
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE
LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE
DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG
KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM
PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US
UZ VC VN YU ZA ZM ZW
ADT WO 2004046314 A2 WO 2003-US36133 20031113
PRAI US 2002-426677P 20021115
IC ICM C12N000-00

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	44.98	200.10

STN INTERNATIONAL LOGOFF AT 07:40:07 ON 25 JUN 2004